

while trying desperately to reduce costs in health care. Perhaps this is all that can be expected until exactly what is meant by quality becomes more tangible and more visible for all to see. Clearly this urgently needs more attention by the medical profession. There just might be a lesson to be learned from the apocryphal Japanese automakers' attention to standards, performance, accountability and esprit among workers to assure quality in spite of lower costs.

—MSMW

Chemicals and the Development of Cancer

IN THE PAST TWO DECADES a radical change in the perception of cancer by the medical profession and by the public at large has occurred. From a disease almost universally viewed as being of unknown origin or causation some three decades ago, cancer has become perceived today as *the* ultimate expression of environmental contamination. This extreme view is very widely held but is perhaps only partially valid.

As clearly stated by Smuckler in this issue and in other recent reviews,¹⁻⁴ many epidemiologic studies, backed by an increasing body of experimental work, have implicated a variety of chemicals (some 30-odd), some viruses and several forms of irradiation, as initiating causes of human cancer. Many cancers of the respiratory tract and some of the genitourinary system, upper gastrointestinal tract, skin and thyroid have environmental components, often chemicals, as important etiologic agents. This has naturally led to the popular thesis that a major advance in cancer prevention will rapidly occur when the offending environmental agents are identified and removed. This is no doubt true in some instances—for instance, smoking and lung cancer, certain chemicals and bladder cancer, vinyl chloride and thorotrast and angiosarcoma of the liver, asbestos and mesothelioma—to name some of the more obvious examples. The exposures to the chemicals in these instances are often intensive or prolonged, or both.

Yet research in the past decade or so has been toward a major modification of this viewpoint, namely that *exposure* to a carcinogen is by no means synonymous with induction of cancer and that the presence of the carcinogen in the environment is but one factor in a multifactorial matrix or network. Although we now appreciate more readily the complex multistep nature of the very long “preneoplastic” or “precancerous” stages in cancer development with chemicals and other agents, evidently even for the very early steps of initiation, such a perspective is more realistic and valid than is the previous simple equation of exposure and risk.

There are at least five interacting segments of a network that determine what effect a certain exposure to a carcinogen might have on initiating the carcinogenic process: (1) concentration and duration of exposure to the carcinogens; (2) the efficiency with which a chemical is metabolized to an active carcinogen or to noncarcinogenic derivatives; (3) the efficiency with which

the target tissue cells are able to “detoxify” carcinogens; (4) the presence and rate of repair of chemical and physical damage to DNA,² and (5) the presence or induction of cell proliferation in target cells.

1. A clear-cut dose response is seen in many instances with chemical carcinogens in humans. For example, with smoking and with occupational exposure to aromatic amines (benzidine, β -naphthylamine), vinyl chloride and the like, a relationship between levels of exposure, duration of exposure and cancer incidence has been documented. With the large number of carcinogens that are found in our environment, however, the dose range is often quite low. Under such circumstances, the other four known factors almost certainly play a determinant role.

2. The metabolic capability for different carcinogens (or, more accurately, “procarcinogens”) varies enormously from tissue to tissue and species to species. In general, humans are quite capable of metabolizing many procarcinogens of different types to active carcinogenic derivatives.^{1,2} The variations in this capacity are no doubt an important factor in determining the organ sites for different carcinogens.

This component of the network is modulated by diet, hormones and genetics. Major positive or negative influences on metabolic activation can be shown for each of these three major types of modulators in animals. Conceivably, the known effects of diet, hormones and genetics on human cancer incidence may be exerted in part on this aspect of carcinogenesis.

3. A factor that is now receiving increasing attention is the efficiency with which cells or tissue can “soak up” or inactivate activated forms of carcinogens. Glutathione and the enzymes glutathione-S-transferase, epoxide hydrolase and glucuronyl transferase, among others, are able to convert active carcinogens to various conjugated forms or to hydrated forms, steps that lead either directly or indirectly to inactivation.⁵ Each tissue has a constellation of enzymes and other components that can readily inactivate active derivatives of potential carcinogens, mutagens and other xenobiotics. Such reactions have been shown to protect cells against damage to DNA and other macromolecules by carcinogens.

4. The efficiency by which damage to DNA is repaired is a critical factor in the genesis of epidermoid carcinoma and melanoma by ultraviolet light in humans (for example, xeroderma pigmentosum). Conceivably the same might also be operating for chemical carcinogens, because virtually every tissue has a spectrum of “repair enzymes.” The exact role of such repair activity in the genesis of cancer by chemicals in humans has yet to be delineated.

5. Cell proliferation is known to be an essential step in the initiation of carcinogenesis with chemicals and probably also with some viruses and radiations. In the liver, pancreas, urinary bladder and other adult “quiescent” tissues, there is good evidence that local tissue damage (such as toxic hepatitis) plays an essential role in starting the carcinogenic process. The tissue damage leads to local cell proliferation and the latter is required

before a chemical can initiate the carcinogenic process in such tissues.

This might well be an important factor in the very high incidence of liver cancer in many countries in Asia and Africa. Although a close association with exposure to hepatitis B virus is now widely appreciated, there is good evidence that liver cell damage may be quite important. Thus, cellular injury induced by any agent or associated with other diseases such as liver cirrhosis, chronic pancreatitis or chronic cystitis might well play important roles in facilitating the initiation of cancer development in the organs or tissues in which normal cell proliferation is minimal or absent.

This shows the type of interplay between known factors that probably plays a role in determining the susceptibility of persons to the carcinogenic consequences of exposure to chemical carcinogens. A similar delineation of important modulating factors might become possible for later steps in the carcinogenic process, such as those associated with promotion and progression. As physicians, the challenge lies in identifying those specific factors that modulate against initiation or subsequent steps in the development of cancer. Their study could well have a major influence in devising a rational and acceptable way to prevent some forms of cancer.

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The Social Transformation of American Medicine

The Social Transformation of American Medicine,¹ a book written by Paul Starr, an Associate Professor of Sociology at Harvard University, should be read and reflected upon by any physician who is in a position

of leadership in our profession in these unsettled days, and by any physician who wishes to know more about how we as a profession have got to where we are. The work is superbly documented and it rings true to one who has been more than casually concerned with developments in medicine and health care over the last quarter century. It is not hostile to medicine. It gives organized medicine its due, but suggests that forces beyond the control of medicine or anyone else have done the most to shape what Starr calls a "sovereign profession" and are now bringing about its "social transformation" into something that yet remains to be seen.

He notes that as medical care has become something worth having and as it has become more costly—it has become "everybody's business" as is evidenced by three "revelations" of the 1970s. The first was a discovery of a "health care crisis" by the liberals which was to open the way for governmental reform of what was touted to be a "new system" of health care. As costs continued to rise, there was a second "revelation": Health care was found hardly to improve health at all and in fact might even be harmful to it. This made the first revelation seem less important and diverted attention to cost control. And the third "revelation," this time espoused by conservatives, revealed that the problems of health care in America could be solved by relying on competition and incentives, if the government's role were reduced to a minimum. At present Starr believes that no group is dominant and that there is no evidence that one approach is better than another. He does suggest that doctors continue to hold a strategic position through their established relationships with patients and hospitals, as they enter the emerging world of zero-sum medical practice and as the new medical corporations hove upon the scene.

While this book offers no clear vision of what the future will be, it does provide insight into the forces that have brought us to our present situation and which may help to shape the further evolution, and likely the transformation, of medical practice and patient care in this nation. It should be required reading for those most concerned with and about these problems.

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